

**REMARKS**

Reconsideration is requested.

The Examiner is requested to return a completely-initialed copy of the PTO-1449 Form bearing the OIPE date-stamped of March 2, 2005. Specifically, page 1 of 3 of the PTO-1449 Form returned with the Office Action of August 21, 2006, does not include the Examiner's initials next to the reference Encell and Loeb. The entirety of the PTO-1449 Form has been initialed by the Examiner on August 16, 2006, and the other references indicated as having been specifically considered by initialing next to each of the references. The Encell and Loeb reference however does not include in the left-hand column the Examiner's initials. A completely-initialed copy of the PTO-1449 Form, pursuant to MPEP § 609, is requested.

Claims 123-179 are pending. Claims 123-164 were elected in the Response of June 23, 2006. Claims 165-179 have been withdrawn from consideration. The Examiner's comments on pages 1-2 of the Office Action dated August 21, 2006 incorrectly list the status of the claims. Correction of the record or further clarification is requested.

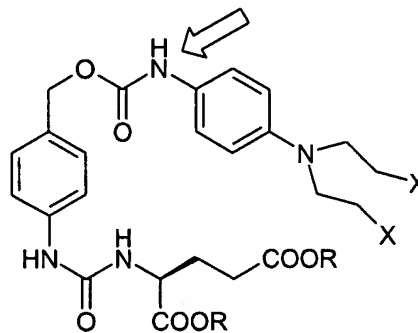
The Section 103 rejection of claims 123-154 and 160-164 over Springer (WO 96/22277 and U.S. Patent No. 6,005,002), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner has raised a single objection (against all elected claims) on the basis of the Springer et al. PCT publication, WO 96/22277 (or the corresponding granted US Patent No 6,005,002).

**Best Available Copy**

The contents of the cited document are described in the present application at page 8, line 10 to page 9, line 2.

A primary difference between the WO 96/22277 compounds and the presently claimed compounds is the presence of an alkyl substituent on the nitrogen atom of the carbamate group, indicated by the arrow in the following structure:

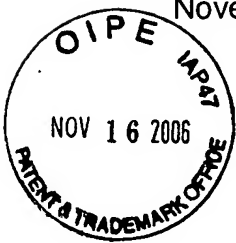


The Examiner is believed to have acknowledged that WO 96/22277 fails to teach or suggest substitution on this nitrogen atom.

The Examiner is understood to be asserting however that Ex parte Bluestone 135 USPQ 199 (1961) allegedly supports a finding that it would have allegedly been *per se* obvious to alter the nitrogen with an alkyl substitution.

The Examiner is urged to see the attached In re Langer and Haynes, 175 USPQ 169 (C.C.P.A. 1972) wherein the Court summarized the issue as follows:

The sole reference relied upon is the Jezl patent. Like appellants, Jezl was concerned with imparting dyeability to poly(alpha-olefins) and discloses accomplishing this by copolymerizing alpha-olefins with alkenyl amines in the presence of a Ziegler-type catalyst. Jezl discloses using terminally unsaturated alkenyl amines and recites a long list of suitable amines. We need not review the many amines disclosed by Jezl for the Board and the solicitor relied on only one, N,N-di-2-ethylhexyl-4-pentenylamine. This is concededly a sterically hindered amine of the type contemplated by appellants, although it does not fall within



the scope of the definition of suitable amines recited in the appealed claims. Appellants assert that the named amine is the only amine disclosed by Jezl which is structurally similar to those found by appellants to be suitable for use with Ziegler-type catalysts, all the other Jezl amines being unhindered. Nothing said by the board in either its original opinion or its opinion pursuant to appellants' request for reconsideration, and nothing argued by the solicitor, is inconsistent with that assertion. The solicitor's case is built entirely on the named amine. We therefore approach this case from the premise that Jezl names one sterically hindered amine for use in the same process as appellants and many other amines, all of which are unhindered. ...

The solicitor asserts that this case should be resolved on the basis of homology of the named amine in Jezl and appellants' amines which compels, in his view, a holding of prima facie obviousness which stands un rebutted.

Appellants urge that Jezl shows no appreciation for the problem solved by them and that as a result, there is no basis for selecting the one amine relied upon and finding the use of sterically hindered amines to have been obvious to one of ordinary skill in the art. Id. at 170-171.

In overturning the Board's affirmation of the obviousness rejection, the Court explained the following regarding alleged *per se* cases of obviousness.

We find ourselves in agreement with appellants' position in this case. As elementary as it may be to patent law under the 1952 Act, the concept of having to show obviousness of the invention "as a whole," as required by 35 U.S.C. 103, is especially appropriate to bear in mind in this appeal. See In re Aufhauser, 55 CCPA 1477, 399 F.2d 275, 158 USPQ 351 (1968); In re Hoeksema, 55 CCPA 1493, 399 F.2d 269, 158 USPQ 596 (1968). That concept supersedes "rules" which might emerge from the repeated application of other principles which may ordinarily be correct but fail under a set of facts which bring such principles in conflict with the broader notions of § 103. So it is that while this court has found the prior art disclosure of homologues of compounds to render prima facie obvious claims to those compounds, see, e.g., In re Ackermann, 58 CCPA 1405, 444 F.2d 1172, 170 USPQ 340 (1971); In re Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (1963), homology should not be

automatically equated with prima facie obviousness. The facts of the present case strain to the breaking point such an equation.

We view appellants' invention "as a whole" as being the use of sterically hindered amines as opposed to unhindered amines in a known process to solve a particular problem. We find no challenge to appellants' contentions that the problem of catalyst deactivation exists and the use of sterically hindered amines as a class solves it. We do not think the Jezl patent provides a basis for the use of sterically hindered amines as a class, or of any of the amines encompassed by appellants' claims, in the Jezl process. The presence in the reference of an isolated hindered amine falling outside the scope of appellants' claims does not, by itself, apprise the ordinary artisan of the significance of hindered amines as a class. Compare *In re Kuderna*, 57 CCPA 1078, 1083-84, 426 F.2d 385, 389, 165 USPQ 575, 578-79 (1970).

This court has said that "[a]ll of the disclosures in a reference must be evaluated for what they fairly teach one of ordinary skill in the art." *In re Boe*, 53 CCPA 1079, 1083, 355 F.2d 961, 965, 148 USPQ 507, 510 (1966). Under the facts in *Boe*, that concept brought non-preferred embodiments within the purview of prior art subject matter against which the claimed subject matter could be compared. However, the concept cuts both ways, and when "all of the disclosures in a reference" are considered, the overall suggestion to emerge from the prior art reference may be contrary to that which might appear from an isolated portion of the reference. Compare *In re Sebek*, 175 USPQ 93, Patent Appeal No. 8631, decided August 31, 1972. In effect, we compare the prior art "as a whole" with the claimed subject matter "as a whole." Doing so in the present case convinces us of the error in the board's decision, and we accordingly reverse.

Similar to the facts considered by the Court in Langer and Haynes, the cited art fails to provide an appreciation for the problem solved by the present application such that there is no motivation in the art to have made the presently claimed invention.

The applicants believe therefore that the Examiner has failed to establish a *prima facie* case of obviousness. The Section 103 rejection should be withdrawn.

For completeness, the applicants provide the following response to the Examiner's comments relating to the present disclosure.

Specifically, the Examiner has commented as follows on some of the evidence of the disclosure (see page 5 of the Office Action dated August 21, 2006):

Based on the above teachings, when a person of ordinary skill in the art examines the data provided by the applicants (Please see: Specification, page nos. 81, 82 Cytotoxicity Data :Table 1 and Table 2), it is not clear to conclude that N-Me or N-substituted compounds has improved activity over unsubstituted compounds. For example, if the results of CP-2 (IC<sub>50</sub> is 179.8 ; Degree of activation (fold) 101.6 ) P-1(IC<sub>50</sub> is 184.7 ; Degree of activation (fold) 124.0) , are compared and CP-2 shows a degree of activation of 101.6 at IC<sub>50</sub> 179.8 and P-2 shows degree of activation of 124.0 at IC<sub>50</sub> 184.7. Is it because the compounds exhibit higher degree of activation at higher concentrations, if it is not so then for the record, the data provided does not adequately teach the superiority of the invention over the prior art.

The Examiner appears to have concluded in the above that

"is not clear to conclude that N-Me or N-substituted compounds [have] improved activity over unsubstituted compounds."

The Examiner further comments that

"it is because the compounds exhibit higher degree of activation at higher concentrations".

The Examiner appears to have perhaps not understood the data of the specification the phrase "degree of activation" and consideration of the following in this regard is requested.

Using the data in Table 1 (at pages 81-82), it is possible to provide two side-by-side comparisons, specifically, for the iodo-para-H/Me compounds and the bromo-para-H/Me compounds.

Considering first the iodo-para-H/Me compounds in the following Table:

Cytotoxicity Data Side-by-Side Comparisons for Iodo-Para-H/Me Compounds								
Cmpd	Z	o/p	R <sup>N</sup>	X <sup>1</sup>	X <sup>2</sup>	IC <sub>50</sub> ( $\mu$ M)		Degree of activation (fold)
						LacZ	stCPG2(Q)3	
<b>P-1</b>	NH	para	Me	I	I	184.7 (105.4-324.4)	1.5 (0.8-2.6)	124.0
<b>CP-2</b>	NH	para	H	I	I	179.8 (71.7-449.4)	1.8 (1.0-3.2)	101.6

wherein P-1 is the prodrug of interest and being claimed, and CP-2 is the corresponding comparison prodrug which is not being claimed. The two compounds differ only in regard to the R<sup>N</sup> group.

The cell line denoted stCPG2(Q)3 stably expresses the prodrug-activating enzyme. For this cell line, much less of the prodrug is required to kill 50% of the cells, because the prodrug-activating enzyme (that converts the prodrug to drug) is abundant.

The cell line denoted LacZ stably expresses a different (non-prodrug-activating) enzyme. For this cell line, much more of the prodrug is required to kill 50% of the cells, because any prodrug-activating enzyme (that converts the prodrug to drug) is scarce.

For example, the prodrug P-1 is "less active" in the LacZ cell line (the IC<sub>50</sub> is higher; more prodrug is needed to kill 50% of the cells) than in the stCPG2(Q)3 cell line (the IC<sub>50</sub> is lower; less prodrug is needed to kill 50% of the cells). This is as intended. The prodrug is "more active" in cell lines that express the activating enzyme.

Comparing P-1 and CP-2 in the LacZ cell line (where the prodrug-activating enzyme is scarce), P-1 is less active than CP-2. This is desirable as it is desirable to not have the prodrug be activated and converted to drug in these cells. In the stCPG2(Q)3 cell line (where the prodrug-activating enzyme is abundant), P-1 is more active than CP-2. This too is desirable – the prodrug is activated and converted to drug in these cells. These two effects are synergistic, and give rise to an overall improvement.

The “degree of activation” (the ratio of IC<sub>50</sub> for the LacZ cell line to the IC<sub>50</sub> for the stCPG2(Q)3 cell line) is a good measure of a prodrug's *ability to work effectively* in enzyme prodrug therapy (EPT). The higher the “degree of activation” the better.

The claimed prodrug P-1 has a “degree of activation” of 124.0 fold.

The comparison prodrug CP-2 has a “degree of activation” of 101.6 fold.

Thus, the claimed prodrug P-1 has a “degree of activation” that is 22% better than the “degree of activation” for the comparison prodrug CP-2.

Thus, the claimed prodrug P-1 is better suited for use in enzyme prodrug therapy (EPT) than the corresponding comparison prodrug CP-2.

This improvement is important and significant as improvements in the “degree of activation” reduce the amount of prodrug that must be administered, and thereby reduce undesired side-effects in the patient.

The same conclusion can be reached for the bromo-para-H/Me compounds. The corresponding data are shown in the following table:

Cytotoxicity Data Side-by-Side Comparisons for Bromo-Para-H/Me Compounds								
Cmpd	Z	o/p	R <sup>N</sup>	X <sup>1</sup>	X <sup>2</sup>	IC <sub>50</sub> ( $\mu$ M)		Degree of activation (fold)
						LacZ	stCPG2(Q)3	
<b>P-2</b>	NH	para	Me	Br	Br	332.4 (222.6-496.3)	4.1 (2.5-6.7)	81.4
<b>CP-4</b>	NH	para	H	Br	Br	204.6 (108.6-384.6)	3.1 (1.8-5.3)	66.6

Again, the above P-2 is a prodrug of interest and CP-4 is the corresponding comparison prodrug which is not a part of the present claims. The two compounds differ only in regard to the R<sup>N</sup> group.

The claimed prodrug P-2 has a "degree of activation" of 81.4 fold and the comparison prodrug CP-4 has a "degree of activation" of 66.6 fold.

Thus, the claimed prodrug P-2 has a "degree of activation" that is 22% better than the "degree of activation" for the comparison prodrug CP-4 and the claimed prodrug P-2 is better suited for use in enzyme prodrug therapy (EPT), than the corresponding comparison prodrug CP-4.

In summary, the cited art fails to teach or suggest the presently claimed invention and the Section 103 rejection should be withdrawn. Moreover, while not required, the data in the application support the conclusion that N-alkylation compounds of the claims demonstrate a greater "degree of activation" which are therefore better suited for use in enzyme prodrug therapy (EPT), than the corresponding N-unsubstituted prodrugs.

Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required in this regard.




SPRINGER et al.  
Appl. No. 10/526,173  
November 16, 2006

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

By: \_\_\_\_\_



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on paper, but are unattainable in any real world. (P. 681.) [Footnote 6 on same page: Let the proponents of a single court of special jurisdiction for patent appeals ponder on the future of the system if the chosen court insists on straitjacketing itself.]

The paucity of cases in which a successful opposition has been followed up is truly amazing. When one considers all of the oppositions that have been sustained by the Patent Office and by the CCPA and then sees how many of the defeated applicants continue to use their marks, apparently without molestation, he is led to wonder what the shooting was about. (P. 680.)

The question is, will the conditions be any different under the Act of 1946? Or will oppositions be treated in the same unreal manner? (P. 681.)

The only conclusion that can be reached is no conclusion at all. The court can go either way. \* \* \* It is this writer's opinion that the unsatisfactory operation of the Act of 1905 was due in no small measure to the rigid interpretation forced upon it by the Court of Customs and Patent Appeals. An equally rigid interpretation will likewise hobble the Act of 1946. (P. 683.)

The first decisions of the court under the new act will reveal whether or not registration is going to be allowed to operate in harmony with the realities of trade. [The end.] (P. 684.)

In my opinion, the facts in this case give rise to an estoppel against Johnson. I would therefore reverse.

### Court of Customs and Patent Appeals

In re LANGER AND HAYNES

No. 8731

Decided Sept. 14, 1972

#### PATENTS

##### 1. Patentability — Composition of matter (§51.30)

##### Patentability — Invention — In general (§51.501)

35 U.S.C. 103 requires that obviousness of invention as a whole be shown; that concept supersedes "rules" which might emerge from repeated application of other principles which may ordinarily be correct but fail under a set of facts which bring such principles in conflict with broader notions of sec-

tion 103; so it is that while court has found the prior art disclosure of homologues of compounds to render prima facie obvious claims to those compounds, homology should not be automatically equated with prima facie obviousness; prior art as a whole is compared with claimed subject matter as a whole.

#### Particular patents—Copolymerization

Langer and Haynes, Copolymerization Process, claims 11 and 14 to 17 of application allowed.

Appeal from Board of Appeals of the Patent Office.

Application for patent of Arthur W. Langer, Jr., and Raymond R. Haynes, Serial No. 467,109, filed June 25, 1965; Patent Office Group 140. From decision rejecting claims 11 and 14 to 17, applicants appeal. Reversed.

DAVID A. ROTH, Elizabeth, N. J. (M. F. FINCKE, S. W. BROCK, JR., JOHN S. SCHNEIDER, and THOMAS B. McCULLOCH, all of Houston, Tex., of counsel) for appellants.

S. WM. COCHRAN (FRED W. SHERLING of counsel) for Commissioner of Patents.

Before RICH, Acting Chief Judge, ALMOND, BALDWIN, and LANE, Associate Judges, and CLARK, Justice, United States Supreme Court (Ret.), sitting by designation.

LANE, Judge.

This is an appeal from that portion of the decision of the Board of Appeals sustaining the examiner in rejecting process claims 11 and 14-17<sup>1</sup> of appellants' application<sup>2</sup> as unpatentable under 35 U.S.C. 103 for obviousness over a patent to Jezl et al. (Jezl).<sup>3</sup> Our review of the record and arguments in this case convinces us that the board erred, and we accordingly reverse.

The claimed invention is a process of copolymerizing an alpha-olefin and a sterically hindered alkenyl amine in the presence of a Ziegler-type catalyst. In the specification, appellants explain that prior to their invention the polymerization of alpha-olefins, such as ethylene and propylene, to form, for example,

<sup>1</sup> On appeal to the board, the application included product claims in addition to these process claims, and the board affirmed the examiner's rejection of the product claims as well. However, appellants have expressly withdrawn the product claims from this appeal.

<sup>2</sup> Serial No. 467,109 filed June 25, 1965.

<sup>3</sup> U. S. Patent No. 3,293,326 issued December 20, 1966, on an application filed July 6, 1965, as a continuation-in-part application of one filed June 17, 1960.



they react. Appellants' was the selection of re sterically hindered which have a structure nt of the component is retarded or inhib-

dest claim on appeal

ation process which under polymerization sence of an organo-al catalyst and [sic] ng 2 to 10 carbon amine having one of e:

ability to poly(alpha- accomplishing this by olefins with alkenyl nce of a Ziegler-type using terminally unsat- and recites a long list e need not review the d by Jezl for the Board on only one, N,N-di-2- amine. This is conced- ered amine of the type llants, although it does ope of the definition of d in the appealed claims. the named amine is the by Jezl which is struc- e found by appellants to h Ziegler-type catalysts, mines being unhindered. board in either its original pursuant to appellants' ration, and nothing ar- is inconsistent with that or's case is built entirely We therefore approach mise that Jezl names one mine for use in the same

process as appellants and many other amines, all of which are *unhindered*.

The board held as follows:

Jezl discloses the use of, inter alia, a[n] N, N-di-2 ethylhexyl-4-pentenyl amine which falls outside the artificial formula of \*\*\* [claim] 11 by having 2 alkyl radicals with a total of 16 carbon atoms instead of the upper limit of 13 set forth in the formula. This illustrative compound is described as producing copolymers with alpha olefins and there is nothing to suggest that it does not do this as effectively as do the homologous unsaturated amines of appellants' claim 5 [which defined the amine as N,N-diisopropyl-3-butenylamine and which was in the group of product claims withdrawn from appeal].

Indeed, it might be expected that the illustrative amine serves more effectively its process and product purpose than many of the amines called for in appellants' claims \*\*\* 11, and 14 to 17 because it is a polymerizable *terminally* unsaturated amine. Jezl et al. specify that their amine monomer must be terminally unsaturated and appellants specifically identify no useful amine having anything other than terminal unsaturation in its alkenyl group.

Appellants' principal argument with respect to Jezl et al. appears to be that the patent does not show the same "structure" as that claimed, by which we assume that appellants refer to their limitation on the total number of alkyl carbon atoms in the amine. This number is not shown to be "critical," or to distinguish the effective, from the ineffective compounds.

The solicitor asserts that this case should be resolved on the basis of homology of the named amine in Jezl and appellants' amines which compels, in his view, a holding of *prima facie* obviousness which stands un rebutted.

Appellants urge that Jezl shows no appreciation for the problem solved by them and that as a result, there is no basis for selecting the one amine relied upon and finding the use of sterically hindered amines to have been obvious to one of ordinary skill in the art.

### Opinion

[1] We find ourselves in agreement with appellants' position in this case. As elementary as it may be to patent law under the 1952 Act, the concept of having to show obviousness of the invention "as a whole," as required by 35 U.S.C. 103, is especially appropriate to bear in mind in this appeal. See *In re Aufhauser*, 55 CCPA 1477, 399 F.2d 275, 158 USPQ 351 (1968); *In re Hoeksema*, 55 CCPA 1493, 399 F.2d 269, 158 USPQ 596 (1968). That concept supersedes "rules" which might

emerge from the repeated application of other principles which may ordinarily be correct but fail under a set of facts which bring such principles in conflict with the broader notions of § 103. So it is that while this court has found the prior art disclosure of homologues of compounds to render *prima facie* obvious claims to those compounds, see, e.g., *In re Ackermann*, 58 CCPA 1405, 444 F.2d 1172, 170 USPQ 340 (1971); *In re Papesch*, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (1963), homology should not be automatically equated with *prima facie* obviousness. The facts of the present case strain to the breaking point such an equation.

We view appellants' invention "as a whole" as being the use of sterically hindered amines as opposed to unhindered amines in a known process to solve a particular problem. We find no challenge to appellants' contentions that the problem of catalyst deactivation exists and the use of sterically hindered amines as a class solves it. We do not think the Jezl patent provides a basis for the use of sterically hindered amines as a class, or of any of the amines encompassed by appellants' claims, in the Jezl process. The presence in the reference of an isolated hindered amine falling outside the scope of appellants' claims does not, by itself, apprise the ordinary artisan of the significance of hindered amines as a class. Compare *In re Kuderna*, 57 CCPA 1078, 1083-84, 426 F.2d 385, 389, 165 USPQ 575, 578-79 (1970).

This court has said that "[a]ll of the disclosures in a reference must be evaluated for what they fairly teach one of ordinary skill in the art." *In re Boe*, 53 CCPA 1079, 1083, 355 F.2d 961, 965, 148 USPQ 507, 510 (1966). Under the facts in *Boe*, that concept brought non-preferred embodiments within the purview of prior art subject matter against which the claimed subject matter could be compared. However, the concept cuts both ways, and when "all of the disclosures in a reference" are considered, the overall suggestion to emerge from the prior art reference may be contrary to that which might appear from an isolated portion of the reference. Compare *In re Sebek*, 175 USPQ 93, Patent Appeal No. 8631, decided August 31, 1972. In effect, we compare the prior art "as a whole" with the claimed subject matter "as a whole." Doing so in the present case convinces us of the error in the board's decision, and we accordingly *reverse*.

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